Can Chronic Opioid Therapy Be Used Safely and Effectively for the Treatment of Chronic Pain?

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Disclosure

- Consultant/Independent Contractor
  - Depomed, Teva, Endo, Purdue, Quest, Grünenthal, Pfizer, Semnur
- Grant/Research Support
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- Speakers Bureau
  - Allergan, Depomed, Xenoprot
- Stock Shareholder
  - Pfizer, Depomed
- Other/Royalty
  - Elsevier
Learning Objectives

- Assess adherence with treatment (may include urine screening)
- List opioid sparing approaches
- Describe a Plan B that includes withdrawal and alternative management approaches
- Explain conversion tables, methods of rotation, specific medical situations
- Apply multimodal therapies for addressing chronic pain

Establishing Realistic Treatment

Outcome Expectations for Analgesic Therapies

- Nonopioid analgesics
- Invasive pain management
- Opioid analgesics
Chronic Opioid Therapy In Chronic Noncancer Pain: Guidelines from the American Pain Society & the American Academy of Pain Medicine

Realistic Individualized Goal-Setting

- Reach agreement with patient on treatment goals
- Patient-specific goals may include 1 or more of the following
  - Pain reduction: 30% considered clinically significant
    - Explain to patient that complete pain relief rarely achieved
  - Improvement in select functional areas:
    - Ability to work full time at previous or modified job, play golf once a week, walk the dog daily, etc
  - Improved mood

Gabapentin in the Treatment of Painful Diabetic Neuropathy*

Should Healthcare Providers Prescribe Opioids for Chronic Pain? Key Considerations

- Adequate training?
- Methods to do so safely in their practice
- Respecting the evidence as well as its limitations for the use of opioid analgesics for chronic pain—especially when used as monotherapy

Should Healthcare Providers Prescribe Opioids for Chronic Pain?

- The question “should” (or should not) a healthcare provider prescribe opioids is a false dichotomy/question! The only question is not should but how well are we prepared to prescribe opioids for the best benefits to our patients with minimal risks
- Healthcare providers through their training and experience as well as their oath to relieve suffering must be able to:
  - Learn how to select patients for opioid therapy, when indicated
  - Manage patients on opioid therapy as safely and effectively as possible
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Academy of Pain Medicine

Roger Chou, MD
Director, American Pain Society Guidelines
Program

April 30, 2009

Goal: define most appropriate treatment regimen for each person in pain, which could include opioids


What is the Evidence?
There is abundant evidence for use of opioid analgesics for chronic pain

AND THERE ARE SERIOUS RISKS:
Opioid Analgesic Overdoses = Public Health Epidemic

- Opioid analgesics are among the most commonly misused or abused pharmaceuticals
- Overdose deaths from prescription painkillers have increased
  - 16,651 in 2010; >4x # in 1999

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**Neuropathic Pain Recommendations of Various Societies**

<table>
<thead>
<tr>
<th>EFNS, European Neurology</th>
<th>Canadian Pain Society</th>
<th>IASP NeuPSIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line</td>
<td>TCA</td>
<td>TCA, SNRI</td>
</tr>
<tr>
<td></td>
<td>GBP/PGB</td>
<td>GBP/PGB</td>
</tr>
<tr>
<td></td>
<td>Lidocaine 5% plaster</td>
<td>Lidocaine SLS</td>
</tr>
<tr>
<td>Second line</td>
<td>SNRI (Opioid)</td>
<td>SNRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Opioid</td>
</tr>
<tr>
<td>Third line</td>
<td>Opioid</td>
<td>Lidocaine 5%</td>
</tr>
<tr>
<td></td>
<td>Lamotrigine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Capsaicin</td>
<td>(except methadone)</td>
</tr>
<tr>
<td>Fourth line</td>
<td>Methadone</td>
<td></td>
</tr>
</tbody>
</table>

EFNS, European Federation of Neurological Societies; IASP, International Association for the Study of Pain; NeuPSIG, Neuropathic Pain Special Interest Group

**Notes:**

- Improper use of any opioid can result in serious side effects, including overdose and death.

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- Rx, prescription; ED/ER, emergency department/emergency room.
- EFNS, European Federation of Neurological Societies; IASP, International Association for the Study of Pain; NeuPSIG, Neuropathic Pain Special Interest Group

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Need to Balance Access to Pain Medications With Abuse Prevention

Reduced access to opioids for legitimate pain problems

Increased rate of misuse, abuse, and diversion


10 Principles of Universal Precautions

1. Diagnosis with appropriate differential
2. Psychological assessment including risk of addictive disorders
3. Informed consent (verbal or written/signed)
4. Treatment agreement (verbal or written/signed)
5. Pre-/postintervention assessment of pain level and function
6. Appropriate trial of opioid therapy adjunctive medication
7. Reassessment of pain score and level of function
8. Regularly assess the “Four A’s” of pain medicine:
   Analgesia, Activity, Adverse Reactions, and Aberrant Behavior
9. Periodically review pain and comorbidity diagnoses, including addictive disorders
10. Documentation

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History of treated substance abuse
Significant family history of substance abuse
Past/comorbid psychological disorder

Moderate Risk

Stratify Risk

Low Risk
- No past/current history of substance abuse
- Noncontributory family history of substance abuse
- No major or untreated psychological disorder

Moderate Risk
- History of treated substance abuse
- Significant family history of substance abuse
- Past/comorbid psychological disorder

High Risk
- Active substance abuse
- Active addiction
- Major untreated psychological disorder
- Significant risk to self and practitioner

Consider referring high-risk patients or any patient you have concerns about to a pain specialist


All Prescribers Play an Active Role in Reducing the Risks Associated With Opioids

- When opioids are being considered as part of a chronic pain treatment plan:
  - Establish diagnosis
  - Perform a history and physical
  - Order and evaluate the results of relevant diagnostic tests
  - Review current and past treatments
  - Complete an appropriate risk assessment PRIOR to prescribing
  - Monitor the patient regularly on an ongoing basis
  - Prescribe opioids as part of a multimodal treatment regimen

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Proposed Critical Thinking Model for Chronic Opioid Therapy

- Patient selection
- Initial patient assessment
- Comprehensive pain management plan
- Trial of opioid therapy
- Patient reassessment
- Implement exit strategy
- Continue opioid therapy
- Alternatives to opioid therapy

When to Consider an Opioid Exit Strategy

- No convincing benefit from opioid therapy despite
  - Dose adjustment
  - Side-effect management
  - Opioid rotation
- Poor tolerance at analgesic dose
- Persistent compliance problems despite
  - Treatment agreement
  - Limits
- Presence of a comorbid condition that makes opioid therapy more likely to harm than help

Opioid Exit Strategy: Possible Paths

- Patient’s behavior consistent with drug addiction
  - Refer for addiction management or comanagement

- Patient unable or unwilling to cooperate with outpatient taper
  - Provide sufficient opioid for 1-month taper or maintain until admission
  - Refer to inpatient or outpatient program or similar service as available

- No apparent addiction problem
  - Taper gradually over 1 month
  - Implement nonopioid pain management (psychosocial support, CBT, PT, nonopioid analgesics)

CBT, cognitive behavioral therapy; PT, physical therapy


Opioid Therapy:
New and Emerging Treatments—Will These Help?

- Abuse resistant
  - Physical barriers
  - If barriers defeated, drug becomes available

- Abuse deterrent
  - Pharmacologic barriers
  - If altered, antagonist or irritant released
Patient Prescriber Agreement (PPA)

- Clinical evidence and guidelines support use of agreements
- Any of following can be used as a PPA:
  - Informed consent documents
  - Treatment agreement documents
  - PPA available for download at no cost*
- Benefits
  - Informed decision making with patient
  - Enables clear and mutual understanding of goals and expectations and respective responsibilities of patient and clinician
  - Can be jointly signed during patient visit

What Is Typically in a Patient Prescriber Agreement (PPA)

- Understanding of risks and benefits of opioid therapy
- Taking the opioid exactly as prescribed
- One prescribing doctor and one designated pharmacy and whether or not refills will be called into pharmacy without an office visit
- Urine/serum drug testing when requested
- Pill counts at each office visit
- No early refills
- How to safeguard their opioids medication
- List of behaviors that may lead to discontinuation of opioids
- Places for signature and dating

Monitoring Patient Adherence

- Level of monitoring depends on risk stratification level determined during initial screening (using ORT or other tools)
  - State PDMPs (Prescription Drug Monitoring Programs)
  - Urine drug testing (UDT)
  - Pill counts
  - Behavioral assessment at each visit
    - If indicated, refer for substance abuse treatment


Monitoring Patient Adherence: Urine Drug Testing (UDT)

- Recommended for all patients for reasons of safety and to remove the stigma associated with UDTs
- Testing does not imply a lack of trust; it is a conversation starter
- Self reports of drug use and behavioral monitoring often fail to detect abuse problems
- UDTs can identify use of prescribed opioids as well as illicit drug use
- Know limitations of UDT or laboratory that you use

Common UDT Scenarios

- One of your patients undergoes UDT in your office and the test is negative for opioids
  - UDTs do differ
  - Certain drugs, including oxycodone, may not be detected by certain laboratory techniques
  - UDT is a conversation starter: “Why do you think your UDT is negative?”
    • Is diversion a possibility?
    • Is he binging and then running out of opioids?
    • Is he failing to take the prescribed drug because symptoms have abated?
    • Do you give him a 30-day Rx supply?


Common UDT Scenarios (cont’d)

- Patient on LA morphine undergoes UDT. Test results positive for morphine and hydromorphone
- Possible explanations include:
  - Patient using another opioid obtained from another physician
  - Hydromorphone is a trace metabolite of morphine found only when very high morphine concentrations are present
Common UDT Scenarios (cont’d)

- Patient being treated with hydrocodone has UDT positive for hydrocodone and hydromorphone
- After hydrocodone use, urine may be positive for:
  - Hydrocodone only
  - Hydrocodone and hydromorphone (metabolite)
  - Hydromorphone only

Common UDT Scenarios (cont’d)

- Patient reports no relief on codeine and UDT is negative
- Possible explanations include
  - Laboratory error
  - Diversion
  - Patient is a slow metabolizer of codeine

Screening vs Confirmatory UDTs

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>Confirmatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis Technique</td>
<td>Immunoassay</td>
<td>GC-MS or HPLC</td>
</tr>
<tr>
<td>Sensitivity (power to</td>
<td>Low or none when testing</td>
<td>High</td>
</tr>
<tr>
<td>detect a class of drugs)</td>
<td>for semi-synthetic or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>synthetic opioids)</td>
<td></td>
</tr>
<tr>
<td>Specificity (power to</td>
<td>Varies</td>
<td>High</td>
</tr>
<tr>
<td>detect an individual</td>
<td>(can result in false-</td>
<td></td>
</tr>
<tr>
<td>drug)</td>
<td>positives or false-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>negatives)</td>
<td></td>
</tr>
<tr>
<td>Turnaround</td>
<td>Rapid</td>
<td>Slow</td>
</tr>
<tr>
<td>Other</td>
<td>Intended for a drug-free</td>
<td>Legally defensible results</td>
</tr>
<tr>
<td></td>
<td>population. May not be</td>
<td></td>
</tr>
<tr>
<td></td>
<td>useful in pain medicine</td>
<td></td>
</tr>
</tbody>
</table>

GC-MS, gas chromatograph mass spectrometer; HPLC, high performance liquid chromatography.

What to Do if Your Patient Needs Treatment for Abuse and Addiction

- Know treatment centers in your area
- Work out a plan with the center you are referring to
- With a clear indication of abuse or addiction, discontinue prescribing of opioids
Referral Sources for Abuse and Addiction Treatment

- Find Substance Abuse and Mental Health Treatment (www.samhsa.gov/treatment)
- National Institute on Drug Abuse (www.nida.nih.gov)
- American Council for Drug Education (www.acde.org)
- American Academy of Addiction Psychiatry
  - Providers’ Clinical Support System for Opioid Therapies (www.pcss-o.org)
  - Providers’ Clinical Support System for Medication Assisted Treatment (www.pcssmat.org)

Patient Counseling Document

Counseling Patients and Caregivers

- Instruct patients to tell you about all medications they are taking
- Warn patients to never abruptly discontinue their opioid if used daily for chronic pain
- Caution patients about all adverse effects including drug-drug interactions
  - Specifically about signs and symptoms of respiratory depression, gastrointestinal obstruction, and allergic reactions
  - Instruct them on when and how to call you about side effects they experience so that you can work with them to manage
  - Side effects can be reported to FDA at 1-800-FDA-1088
- Caution patients to never share their opioids with ANYONE
- Counsel patients about the risk of falls, working with heavy machinery and driving
- Advise patients to store their medication carefully and dispose of safely when no longer needed
  - Medication Guides typically include specific disposal information

Why is patient and caregiver education so important?
Patient Education and Counseling Works!

- Utah Department of Health statewide program demonstrated effectiveness of patient education to reduce unintentional deaths from prescription opioids
  - Media campaign “Use Only As Directed” from May 2008 to May 2009, including:
    - Television and radio spots
    - Distribution of opioid prescribing guidelines and copies of print materials (bookmarks, patient information cards, educational posters)
- Results:
  - In 2008-2009, 14% decrease in unintentional overdose deaths from prescription opioids compared with 2007

Cytochrome P450 Enzymes

- Account for almost 50% of overall elimination of commonly used drugs, including:
  - Statins
  - SSRIs
  - Calcium channel blockers
  - Benzodiazepines
  - Beta blockers
  - Opioids
  - Warfarin
- CYP450 drug-drug interactions often clinically relevant
  SSRI, selective serotonin reuptake inhibitor.


Opioids and CYP450 Interactions

- Pharmacokinetic drug-drug interactions can cause higher or lower blood levels of opioid than expected and result in:
  - Excess opioid effects (including fatal toxicity)
  - Loss of analgesia
  - Misinterpretation of drug tests


Opioids and CYP450 Enzyme Interactions

- Metabolism of several commonly used opioids occurs through enzyme CYP3A4, but CYP2D6 is also important
  - 3A4 is a potent inactivation enzyme
  - 2D6 is an activating enzyme
- Inhibition
  - Can increase drug plasma levels, resulting in greater drug-related effects
- Stimulation
  - Can decrease drug plasma levels and decrease drug-related effects
- However, if an agent is a pro-drug, an inhibitor can decrease drug effects, while an inducer increases the rapidity with which the active compound enters the bloodstream
- Refer to product-specific information for specific opioid-DDIs before prescribing

Overview of Opioid Metabolism

<table>
<thead>
<tr>
<th>Active Components</th>
<th>Metabolism (CYP450)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Not significantly metabolized by CYP450</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>Not significantly metabolized by CYP450</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>Not significantly metabolized by CYP450</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Not significantly metabolized by CYP450</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>2D6, 3A4</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>3A4</td>
</tr>
<tr>
<td>Hydrocodone + Acetaminophen</td>
<td>2D6, 3A4</td>
</tr>
<tr>
<td>Tramadol</td>
<td>2D6, 3A4</td>
</tr>
<tr>
<td>Codeine</td>
<td>2D6</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>3A4</td>
</tr>
<tr>
<td>Methadone</td>
<td>3A4, 2B6, 2D6, 2C9, 2C19</td>
</tr>
<tr>
<td>Oxycodone + Acetaminophen</td>
<td>2D6, 3A4</td>
</tr>
</tbody>
</table>

www.accessdata.fda.gov

Interactions With Other Agents and Substances

<table>
<thead>
<tr>
<th>Agent</th>
<th>Concomitant Use With:</th>
<th>Potential Effect on Opioid Levels and Other Effects</th>
</tr>
</thead>
</table>
| Avinza (morphine sulfate ER capsule) | • Alcohol  
• PGP inhibitors (quinidine) | ↑ (potentially fatal dose)  
↑ |
| Belbuca (buprenorphine buccal film) | • CNS depressants and benzodiazepines  
• CYP3A4 inhibitors  
• CYP3A4 inducers  
• Class IA and III antiarrythmics, other potentially arrhythmogenic agent | Respiratory depression ↑  
↓  
QTc prolongation and torsade de pointe risk ↑ |
| Butrans (buprenorphine transdermal system) | • CYP3A4 inhibitors  
• CYP3A4 inducers  
• Benzodiazepines  
• Class IA and III antiarrythmics, other potentially arrhythmogenic agent | Respiratory depression ↑  
↑  
QTc prolongation and torsade de pointe risk ↑ |
| Dolophine* (methadone HCl tablets) | • CYP450 inducers  
• CYP450 inhibitors  
• Antiretroviral agents  
• Benzodiazepines  
• Potentially arrhythmogenic agents | Mixed effects on levels  
Respiratory depression ↑  
QTc prolongation and torsade de pointe risk ↑ |

*Pharmacokinetic drug-drug interactions with methadone are complex. Refer to package insert for additional information.

www.accessdata.fda.gov

Interactions With Other Agents and Substances (cont’d)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Concomitant Use With:</th>
<th>Potential Effects on Opioid Levels and Other Effects</th>
</tr>
</thead>
</table>
| Duragesic (fentanyl transdermal system) | • CYP3A4 inhibitors  
• CYP3A4 inducers | ↑                                                   |
| Embeda (morphine sulfate ER-naltrexone capsules) | • Alcohol  
• PGP inhibitors (quinidine) | ↑ (potentially fatal dose) |
| Exalgo (hydromorphone HCl ER tablets) | None |                                                      |
| Hysingla ER (hydrocodone bitartrate ER tablets) | • CYP3A4 inhibitors  
• CYP3A4 inducers | ↑                                                   |
| Kadian (morphine sulfate ER capsules) | • Alcohol  
• PGP inhibitors (quinidine) | ↑ (potentially fatal dose) |
| MS Contin (morphine sulfate CR tablets) | • PGP inhibitors (quinidine) | ↑                                                   |
| Nucynta ER (tapentadol HCl ER tablets) | • Alcohol  
• MAOIs | ↑ (potentially fatal dose) Contraindicated in patients taking MAOIs |
| Opana ER (oxymorphone HCl ER tablets) | • Alcohol | ↑ (potentially fatal dose) |
| OxyContin (oxycodone HCl CR tablets) | • CYP3A4 inhibitors  
• CYP3A4 inducers  
• 2D6 inhibitors  
• 2D6 inducer | ↑  
Increased effect |
| Targiniq ER (oxycodone HCl / naloxone HCl) | • CYP3A4 inhibitors  
• CYP3A4 inducers | ↑                                                   |
| Zohydro ER (hydrocodone bitartrate ER capsules) | • CYP3A4 inhibitors  
• CYP3A4 inducers | ↑                                                   |

FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics.  
**Drug Interactions Between Methadone or Buprenorphine and Select Medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT</td>
<td>Increase in AZT concentrations; possible AZT toxicity</td>
<td>No clinically significant interaction</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir</td>
<td>Opiate withdrawal may occur</td>
<td>No clinically significant interaction</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Opiate withdrawal may occur</td>
<td>Opiate withdrawal may occur</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Increased methadone plasma concentrations</td>
<td>Increased methadone plasma concentrations</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>No associated adverse drug interactions</td>
<td>No clinically significant interaction</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Potentially increases duloxetine exposure</td>
<td></td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>Associated with delirium</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>No clinically significant interaction</td>
<td>No clinically significant interaction</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Associated with opiate withdrawal</td>
<td>Not studied</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>No clinically significant interaction</td>
<td>No clinically significant interaction</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>May have synergistic depressant effect</td>
<td></td>
</tr>
</tbody>
</table>


**During Treatment...**

- Keep accurate records
- Assess adherence with treatment (may include urine screening); watch for aberrant drug-seeking behavior
- Acknowledge and “deal with” adverse effects
- Have a Plan B that includes withdrawal and alternative management approaches
- Be prepared to re-examine diagnosis as well as treatment plan!
- Understand conversion tables, methods of rotation, specific medical situations (e.g., kidney and liver failure)
Conclusions

- Safe and effective treatment of chronic pain is an urgent need—many people experience chronic pain DESPITE treatment
- Multimodal therapies for addressing pain are available—opioid sparing approaches are preferred
- Accurate assessment is important for diagnosis and risk stratification
- Many resources are available to assist clinicians